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PATENT SPECIFICATION

Inventor: ELWYN ROBERTS

817,749

Date of filing Complete Specification July 11, 1950.

Application Date July 18, 1949. *No. 18892/49.*

Complete Specification Published Aug. 6, 1959.

Index at acceptance: —Class 2(3), C2(A1 : B38 : T21).

International Classification: —C07c.

COMPLETE SPECIFICATION

Preparation of Substituted Guanidines

SPECIFICATION NO. 817,749

INVENTOR: ELWYN ROBERTS

By a direction given under Section 17(1) of the Patents Act 1949 this application proceeded in the name of National Research Development Corporation, a British corporation established by statute, of 1, Tilney Street, London, W.1.

THE PATENT OFFICE,
6th August, 1959

DB 18322/1(17)/3814 150 7/59 R

In that process the aminating agent is of course ammonia and I have now discovered that by using certain other aminating agents, substituted guanidines may also be prepared.

According to the process of the present invention therefore, I react an O-alkyl iso-urea alkyl hydrogen sulphate (produced by the alkylation of urea with a dialkyl sulphate) with an amine of the general formula:—

$$R.NH_2$$

where R denotes an alkyl, amino, hydroxy-alkyl or amino-alkyl radical (thus $R.NH_2$ may be hydrazine) with the aid of heat to yield a substituted guanidinium salt, and then where necessary, the free base is isolated therefrom.

The amination according to the invention may advantageously be carried out by heating a moderate excess of the amine (of the order of about 20%) with an aqueous solution of the O-alkyl iso-urea salt, for instance, the O-ethyl iso-urea ethyl hydrogen sulphate, to a moderately elevated temperature, for example, to about 60° C.

The free base may be isolated from the resulting solution by the method described in Specification No. 8979/49 (Serial No. 817,748). For example, the product which is a substituted guanidinium alkyl sulphate, may be treated in alcoholic solution with an alkali metal alcoholate, the precipitated alkali made up to a volume of 1,000 c.c. with water, except in the case of Example 5.

In these examples, the free base was not usually isolated as such—except in Example 5, where it is isolated as the bicarbonate—but the yield thereof was estimated by addition of 5 c.c. of the solution to 100 c.c. saturated ammonium picrate solution, the precipitated picrate being filtered, dried and weighed.

The picrates obtained were purified by recrystallisation from a suitable solvent and their identities confirmed by melting point determination.

Example 1

METHYL GUANIDINE

O-ethyl-iso-urea-salt - 500 c.c. ≡ 36.7 g.
Methylamine (7.58N) - 66 c.c.
Yield of methyl guanidine - - 59% of theory

Picrate, recrystallised from aqueous alcohol, m.p. 200° C.

Example 2

ETHYL GUANIDINE

O-ethyl iso-urea salt 250 c.c. ≡ 25.9 g.
Ethylamine (7N) - 86 c.c.
Yield of ethyl guanidine 77% of theory

Picrate, recrystallised from water, m.p. 177° C.

PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Preparation of Substituted Guanidines

I, MINISTER OF SUPPLY, of Shell Mex House, Strand, London, W.C.2, do hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the production of substituted guanidines or salts thereof.

In the specification of my co-pending application No. 8979/49 (Serial No. 817,748) I have described a process for the production of guanidine by etherifying urea to form an iso-urea ether, aminating a salt thereof to yield a guanidinium salt and isolating the free base therefrom.

In that process the aminating agent is of course ammonia and I have now discovered that by using certain other aminating agents, substituted guanidines may also be prepared.

According to the process of the present invention therefore, I react an O-alkyl iso-urea alkyl hydrogen sulphate (produced by the alkylation of urea with a dialkyl sulphate) with an amine of the general formula:—

$$R.NH_2$$

where R denotes an alkyl, amino, hydroxy-alkyl or amino-alkyl radical (thus $R.NH_2$ may be hydrazine) with the aid of heat to yield a substituted guanidinium salt, and then where necessary, the free base is isolated therefrom.

The amination according to the invention may advantageously be carried out by heating a moderate excess of the amine (of the order of about 20%) with an aqueous solution of the O-alkyl iso-urea salt, for instance, the O-ethyl iso-urea ethyl hydrogen sulphate, to a moderately elevated temperature, for example, to about 60° C.

The free base may be isolated from the resulting solution by the method described in Specification No. 8979/49 (Serial No. 817,748). For example, the product which is a substituted guanidinium alkyl sulphate, may be treated in alcoholic solution with an alkali metal alcoholate, the precipitated alkali alkyl sulphate is separated by filtration, and the substituted guanidine obtained as residue after evaporating the solvent alcohol under reduced pressure.

The invention will now be more particularly described and illustrated with reference to the following examples.

In the examples, the general method consists in heating either 250 or 500 c.c.s of an aqueous solution containing the specified amount of ethyl iso-urea ethyl hydrogen sulphate—obtained by the alkylation of urea with diethyl sulphate—with a 20 per cent excess of the requisite amine for three hours at 60° C.

The resulting solution was cooled and made up to a volume of 1,000 c.c. with water, except in the case of Example 5.

In these examples, the free base was not usually isolated as such—except in Example 5, where it is isolated as the bicarbonate—but the yield thereof was estimated by addition of 5 c.c. of the solution to 100 c.c. saturated ammonium picrate solution, the precipitated picrate being filtered, dried and weighed.

The picrates obtained were purified by recrystallisation from a suitable solvent and their identities confirmed by melting point determination.

EXAMPLE 1

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Methylamine (7.58N) - 66 c.c.
Yield of methyl guanidine - - 59% of theory

Picrate, recrystallised from aqueous alcohol, m.p. 200° C.

EXAMPLE 2

ETHYL GUANIDINE

O-ethyl iso-urea salt 250 c.c. ≡ 25.9 g.
Ethylamine (7N) - 86 c.c.
Yield of ethyl guanidine 77% of theory

Picrate, recrystallised from water, m.p. 177° C.

EXAMPLE 3

β-HYDROXYETHYL GUANIDINE

O-ethyl iso-urea salt - 250 c.c.≡25.9 g.
Ethanolamine - - 36 g.

Yield was not estimated owing to high solubility of the picrate in water.

Picrate, recrystallised from boiling water, m.p. 148—9° C.

EXAMPLE 4

N:N'-DIGUANYL ETHYLENEDIAMINE

O-ethyl iso-urea salt - 250 c.c.≡25.9 g. (2 mols)
Ethylene diamine hydrate - - - - 14.5 g.
Yield of N:N'-Diguanyl ethylene diamine - 76%

Picrate, after three recrystallisations from water, m.p. 272° C. with decomposition. The product was probably contaminated with ethylene diamine picrate, which would account for the low value for the melting point.

EXAMPLE 5

O-ethtyl iso-urea salt - 500 c.c.≡36.7 g.
Hydrazine hydrate (59% N_2H_4) - - 30 g.

The solution after reaction at 60° C. for three hours was dark brown in colour. After addition of sufficient N sodium hydroxide solution to neutralize all ethyl hydrogen sulphate the solution was cooled in ice and saturated with carbon dioxide. Deposition of amino-guanidine bicarbonate occurred. The mixture stood in a refrigerator overnight and was then filtered. The product was a greyish powder. After washing with ice-water it was dried in air.

Yield 40 g.=70% of theory.

The mother liquor gave no further yield of amino-guanidine bicarbonate on treatment with carbon dioxide at 0° C.

Substituted guanidines are of interest in the explosive field, in chemotherapy and the dyestuffs industry.

WHAT I CLAIM IS:—

1. A process for the production of a substituted guanidine wherein an O-alkyl iso-urea alkyl hydrogen sulphate produced by the alkylation of urea with a dialkyl sulphate is reacted with an amine of the general formula $R.NH_2$ in which R denotes an alkyl, amino, hydroxy-alkyl or amino-alkyl radical, with the aid of heat to form an R-substituted guanidinium alkyl sulphate.

2. A process as claimed in Claim 1, wherein the R-substituted guanidinium alkyl sulphate is decomposed by alcoholic alkali metal hydroxide and the R-substituted guanidine isolated from the solution.

3. A process as claimed in Claim 1, wherein an O-ethyl iso-urea alkyl hydrogen sulphate is reacted with methylamine to form a salt of methyl guanidine and, if necessary, the said salt is decomposed by alkali metal hydroxide to liberate methyl guanidine which is then isolated.

4. A process as claimed in Claim 1, wherein an O-ethyl iso-urea alkyl hydrogen sulphate is reacted with ethylamine to form a salt of ethyl guanidine and, if necessary, ethyl guanidine is then liberated by alkali metal hydroxide and isolated.

5. A process as claimed in Claim 1, wherein an O-ethyl iso-urea alkyl hydrogen sulphate is reacted with ethtanolamine and the β-hydroxyethyl guanidine salt then decomposed by alkali metal hydroxide to yield the free base.

6. A process as claimed in Claim 1, wherein an O-ethyl iso-urea alkyl hydrogen sulphate is reacted with ethylene-diamine hydrate and the N:N'-diguanyl-ethylene-diamine salt then decomposed to yield the free base.

7. A process as claimed in Claim 1, wherein an O-ethyl iso-urea alkyl hydrogen sulphate is reacted with hydrazine hydrate and the product is decomposed by sodium hydroxide solution and then reacted with carbon dioxide to form amino-guanidine-bicarbonate.

8. A process for the production of substituted guanidines and/or salts thereof, substantially as hereinbefore described with reference to the examples.

9. A process for the production of methyl guanidine, ethyl guanidine, β-hydroxyethyl guanidine, or diguanyl ethylene-diamine substantially as hereinbefore described.

10. A process for the production of amino-guanidine substantially as hereinbefore described.

11. Substituted guanidines and/or salts thereof whenever prepared by any of the processes hereinbefore particularly described.

C. E. BELL,
Chartered Patent Agent,
Agent for Applicant.

PROVISIONAL SPECIFICATION

Preparation of Substituted Guanidines

I, MINISTER OF SUPPLY, of Shell Mex House, Strand, London, W.C.2, do hereby declare the nature f this invention to be as follows:—

This invention relates to the production of substituted guanidines.

In the specification of my co-pending application No. 8979/49 (Serial No. 817,748) I have described a process for the production of guanidine by etherifying urea to form an isourea ether, aminating a salt thereof in aqueous medium to yield a guanidinium salt

and isolating the free base therefrom.

In this process the aminating agent is of course ammonia and I have now discovered that by using certain other aminating agents, substituted guanidine may also be prepared.

According to the process of the present invention therefore, I react a salt of O-alkyl isourea (isourea ether) with an amine of the general formula:—

$$R.NH_2$$

where R denotes alkyl, amino, hydroxy alkyl or amino alkyl in aqueous medium to yield a substituted guanidinium salt, and I then where necessary, isolate the free base therefrom.

The amination according to the invention may advantageously be carried out by heating a moderate excess of the amine (of the order of about 20%) with an aqueous solution of the O-alkyl isourea salt, to a moderately elevated temperature, for example, to about 60° C.

The free base may be isolated from the resulting solution by the method described in Specification No. 8979/49 (Serial No. 817,748).

The invention will now be illustrated with reference to the following examples.

In the examples, the general method consisted of heating 250 or 500 c.c.s of an aqueous solution containing varying amounts of ethyl isourea ethyl hydrogen sulphate—obtained by the alkylation of urea with diethyl sulphate—with a 20 per cent excess of the requisite amine for three hours at 60° C.

The resulting solution was cooled and made up to a volume of 1000 c.c. with water, except in the case of Example 5.

In these examples, a free base was not usually isolated as such—except in Example 5, where it is isolated as the bicarbonate—but the yield thereof was estimated by addition of 5 c.c. of the solution to 100 c.c. saturated ammonium picrate solution the precipitated picrate being filtred, dried and weighed.

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Example 1.

METHYL GUANIDINE.

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Methylamine (7.58N)	66 c.c.
Yield of methyl guanidine	59 per cent of theory

Picrate, recrystallised from aqueous alcohol, m.p. 200° C.

Example 2.

ETHYL GUANIDINE

O-ethyl isourea salt	250 c.c.≡25.9 g.
Ethylamine (7N)	86 c.c.
Yield of ethyl guanidine	77 per cent of theory

Picrate, recrystallized from water, m.p. 177° C. Yield was not estimated owing to high solubility of picrate in water. Picrate, recrystallised from boiling water, m.p. 148—9° C.

Example 3

β-HYDROXYETHYL GUANIDINE

O-ethyl isourea salt	250 c.c.≡25.9 g.
Ethanolamine	36 g.

Example 4.

N:N¹-DIGUANYL ETHYLENEDIAMINE

O-ethyl isourea salt	250 c.c.≡25.9 g. (2 mols)
Ethylene diamine hydrate	14.5 g. (105 mols)

Yield of N:N¹—diguanyl ethylene diamine, 76 per cent.

Picrate, after three recrystallisations from water m.p. 272° C. with decomposition. The product was probably contaminated with ethylene diamine picrate, which would account for the low value of the melting point

Example 5.

AMINO GUANIDINE.

O-ethyl isourea salt	500 c.c.≡36.7 g.
Hydrazine hydrate (59% N_2H_4)	30 g.

The solution after reaction at 60° C. for three hours was dark brown in colour. After addition of sufficient N sodium hydroxide solution to neutralise all ethyl hydrogen sulphate the solution was cooled in ice and saturated with carbon dioxide. Deposition of amino-guanidine bicarbonate occurred. The mixture stood in a refrigerator overnight and

was then filtered. The product was a greyish powder. After washing with ice-water it was dried in air.

Yield 40 g.≡70% of theory.

The mother liquor gave no further yield of aminoguanidine bicarbonate on treatment with carbon dioxide at 0° C.

Substituted guanidines are of interest in the explosive field, in chemotherapy and the dyestuffs industry.

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Agent for the Applicant.

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